

Headaches Associated with Seizure: A Prospective Comparative Cohort Study

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ABSTRACT

Introduction: The purpose of the present study is to examine the frequency of headaches based on their relationship with seizures in epileptic patients as well as types of these headaches, and their clinical characteristics.

Methods: 100 patients with epilepsy (60 female, 40 male), who applied to the epilepsy outpatient clinic of Faculty of Medicine of Uludağ University, were included in the study after accepting their consent forms. Patients with symptomatic epilepsy, secondary headaches and mental retardation were excluded from the study. Patients with epilepsy were divided into two groups as the patients with or without headaches associated with seizure. In addition, according to their temporal relationships with seizures, headaches were grouped as preictal, ictal and postictal headaches and the characteristics of headaches associated with seizure were examined and the patients with and without headache associated with seizure were compared in terms of their demographic and clinical features.

Results: In this study, the prevalence of headache associated with seizure

was found as 42%. Headaches associated with seizure were more frequent in the postictal period and they were mostly characterized as migraine-like headache. According to the seizure periods, 22 (52.3%) of the patients experienced pain during every seizure period. It was determined that preictal headache was frequently migraine-like compared to postictal headache and this headache was more frequently accompanied by aura.

Conclusion: Headache and epilepsy are the most frequent paroxysmal neurological conditions. However, because the symptoms of epilepsy are more remarkable, and its clinical presentation has a more dramatic picture, additional neurological conditions may be overlooked. Since both epilepsy and headache symptoms decrease the quality of life, it is important to treat both conditions. Examination of the correlation between these two situations can guide the physicians for selecting the treatment type, as well as helping them to improve the quality of life.

Keywords: Headaches associated with seizure, epilepsy, migraine-like headaches

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INTRODUCTION

Headache and epilepsy are two common neurological disorders affecting individuals of all ages throughout the world, and their relationship remains controversial. Numerous studies have been conducted to investigate whether there is a connection between these two conditions (1-6).

Headaches can be classified as interictal headaches and peri-ictal headaches according to their temporal (time-wise) relationship with seizures. While interictal headaches do not occur in relation to seizures, peri-ictal headaches are defined as preictal, ictal and postictal headaches according to their time of occurrence relative to seizures (7, 8).

Although the coexistence of epilepsy and headache is common, headache symptoms accompanying seizures are mostly overlooked due to the clinical significance and severity of the seizures. In this study, we aimed to investigate the frequency of headaches and the clinical features of these headaches according to their temporal relationship with epilepsy seizure.

METHODS

This study included 100 patients with epilepsy (60 females, 40 males) between 13 and 66 years of age who applied to the Epilepsy Polyclinic of Uludağ University Faculty of Medicine. Patients with symptomatic epilepsy, secondary headaches and mental retardation were excluded. The study was

approved by the Uludağ University Faculty of Medicine Ethics Committee with decision number: 2005-18/29 and written informed consent forms were obtained from all patients.

According to the temporal relationship with seizures, headaches were classified into three periods, preictal, ictal and postictal headache. The patient's headache was defined as preictal headache if it began within 24 hours before the seizure and continued until the onset of the seizure. The headache that began within three hours following the seizure and resolved within 72 hours after the onset of the seizure were defined as postictal headache (9-12).

The International League Against Epilepsy (ILAE) classification criteria (13) were used for the diagnosis of epilepsy; the International Headache Society (IHS) criteria (12) were used for the diagnosis of migraine. Other types of primary and secondary headaches associated with seizure that did not meet the IHS-3 beta migraine criteria were classified as "other headaches associated with seizure". Seizure types were determined according to EEG findings and anamnesis.

Pain severity during headache attacks were determined using a visual analogue scale (VAS), which was administered according to the patient's

own assessment (14). The patients were asked to score the severity of pain between 1 and 10, with a minimum of 1 and a maximum of 10 points. Headaches associated with seizure was classified as “always” if it occurred in all seizures, “often” if it accompanied more than two-thirds of the seizures, and “rare” if it was less frequent.

All patients included in the study were evaluated according to gender, age, duration of epilepsy, seizure frequency, epilepsy syndrome, seizure types, number of antiepileptic drugs, seizure onset age, frequency of headache, severity, duration, accompanying symptoms (photophobia, phonophobia, nausea, vomiting, throbbing feature), pain severity, migraine and epilepsy history.

Statistical analysis

Statistical analysis of the study data was performed with SPSS (version 13.0) for Windows. All data are presented as mean \pm standard deviation (mean \pm SD). After the Shapiro-Wilk test was used to determine whether data showed normal distribution, t-test was used for the comparison of data of two groups with normal distribution, while the Mann-Whitney U and Kruskal-Wallis tests were used to compare groups without normal distribution. Pearson chi-square test and Fisher's exact chi-square test were used to analyze categorical data. A p-value of <0.05 was considered significant in all statistical analyses.

RESULTS

Forty-two (42%) of the epileptic patients had headache associated with seizure. Of these patients, 27 (65%) were female and 15 (35%) were male. The mean age was 34.4 ± 13.2 years. The mean age of onset of disease was 14.09 ± 10.4 years, mean duration of disease was 19.8 ± 11.1 years, and mean duration of treatment was 19.9 ± 10.6 years. Twenty-eight patients were receiving monotherapy and 14 patients were receiving polytherapy. Twenty-seven patients had focal and 15 patients had generalized epilepsy. The mean pain intensity of headaches associated with seizure according to VAS was 5.5 ± 2.2 . Fifty-eight patients did not describe headache associated with seizure. Demographic and clinical characteristics of patients with headache associated with seizure are given in Table 1.

Five patients had preictal headache, 32 patients had only postictal headache, and five patients had both preictal and postictal headache. None of the patients in this study had ictal headaches.

When patients with only preictal headache were compared to patients with only postictal headache in terms of migraine-like headache frequency, although preictal headache was associated with a higher rate of migraine-like headache, no statistically significant difference was observed. Among our patients, a total of 5 patients (including three with preictal headache, one with postictal headache and one with both preictal and postictal headache) were found to have aura with their headache associated with seizure. It was observed that aura was more frequently associated with preictal headache (preictal 40%, postictal 3.1%) than postictal headache, which was statistically significant ($p=0.005$). There was no statistical significance when focal and generalized epilepsy types were compared according to the frequency of headache associated with seizure (Table 2).

According to IHS criteria, 19 (19%) of the patients had migraine-like headache associated with seizures and 23 patients (23%) had “other types” of headaches. In our study, when patients with migraine-like headache associated with seizures, patients who had other types of headaches associated with seizures and those who did not have headaches were compared, no statistically significant differences were terms of gender, age, seizure onset age, duration of epilepsy, frequency of seizures and

Table 1. Demographic and clinical characteristics of patients with seizure-related headache

Female/Male (n)		27/15
Average age (mean \pm sd years) (min-max)		34.4 ± 13.2 (13–64)
Mean age of disease onset (mean \pm sd years) (min-max)		14.09 ± 10.4 (0–41)
Mean disease duration (mean \pm sd years) (min-max)		19.8 ± 11.1 (1–50)
Mean treatment time (mean \pm sd) (min-max)		19.9 ± 10.6 (1–50)
Severity (according to VAS) (mean \pm sd) (min-max)		5.5 ± 2.2 (3–10)
Treatment	Monotherapy	28
	Polytherapy	14
Seizure type	Focal	27
	Simple partial	6
	Complex partial	9
	Secondary generalized tonic clonic	21
	Generalized	15
	Primary generalized tonic clonic	15
	Absence	2
	Myoclonic	2

max, maximum; min, minimum; n, number of persons; mean, mean; sd, standard deviation.

antiepileptic drug used. When the patients with and without headache associated with seizure were compared in terms of the presence of migraine and epilepsy in the family, no statistically significant difference was observed (Table 3).

When the 42 patients with headache associated with seizure were examined for pain frequency, it was determined that pain was present in all seizure periods in 22 patients (52.3%), pain was frequently present in 2 patients (4.7%) and pain was rarely seen in 18 (42.8%) patients. On the other hand, in patients with migraine-like headache associated with seizures, the headache complaint was present in every seizure period in 14 patients (73.7%). Whereas, in the group with other types of headaches associated with seizure it was observed that only 8 (34.8%) of the patients had headaches accompanying all seizures.

Interictal migraine was present in 8 of the 19 patients (42.1%) with migraine-like headache associated with seizures, in one of 23 patients (4.3%) with other headaches, and in 12 (20.7%) of the 58 patients without headache associated with seizures. In the present study, when patients with migraine-like headaches were compared with patients with and without other headaches associated with seizures, we found that interictal migraine was more common in patients with migraine-like headache associated with seizures ($p<0.05$).

Table 2. Characteristics of preictal and postictal headache and comparison in terms of epilepsy syndromes

	Preictal headache (n=5)	Postictal headache (n=32)	p value*
Migraine-like headache n (%)	4 (80%)	12 (37.5%)	0.144
Other headaches n (%)	1 (20%)	20 (62.5%)	0.144
Aura n (%)	3 (40%)	1 (3.1%)	0.005
Focal seizure n (%)	3 (60%)	22 (67%)	1
Generalized seizure n (%)	2 (40%)	10 (33%)	1

* Fisher's exact chi-square test

Table 3. Demographic and clinical characteristics of patients with headache associated with seizure types and without headache

		Migraine-like headache associated with seizures (n=19)	Other headaches associated with seizures (n=23)	No headache (n=58)	p value
Gender n (%)	Female	10 (52.6%)	17 (73.9)	25 (43.1%)	0.284*
	Male	9 (47.4%)	6 (26.1%)	33 (56.9%)	
Age (mean \pm sd) (min-max)		34.1 \pm 12.03 (19–63)	34.4 \pm 14.7 (13–64)	33.4 \pm 14.5 (16–66)	0.830**
Epilepsy duration (mean \pm sd) (min-max)		20 \pm 14.1 (1–50)	19 \pm 7.6 (4–31)	20 \pm 11.9 (1–52)	>0.05**
Seizure frequency n (%)	No seizures for the last 1 year	5 (26.3%)	12 (52.2%)	26 (44.8%)	0.386*
	Monthly <1	6 (31.6%)	7 (30.4%)	15 (25.9%)	
	Monthly >1	8 (42.1%)	4 (17.4%)	17 (29.3%)	
Number of antiepileptic drugs (mean \pm sd) (min-max)		1.57 \pm 0.76 (1–3)	1.43 \pm 0.84 (1–4)	1.55 \pm 0.77 (0–5)	0.662**
Age of seizure onset (mean \pm sd) (min-max)		13.9 \pm 7.54 (2–27)	14.5 \pm 12.5 (0–41)	13.6 \pm 11.6 (0–44)	0.441**
Family history of migraine		6 (31.6%)	2 (8.7%)	12 (20.7%)	>0.05***
Family history of epilepsy		5 (26.3%)	4 (17.4%)	11 (19%)	>0.05***

mean mean; SD, standard deviation. min, minimum; max, maximum

* According to the Pearson chi-square test.

** Kruskal-Wallis Test.

*** Fisher's exact chi-square test.

No statistically significant difference was observed between patients with and without headache associated with seizure in terms of family history of migraine and family history of epilepsy ($p>0.05$).

DISCUSSION

The frequency of headaches associated with seizure was reported to be between 34% and 51% in previous studies, and it was reported that headaches were mostly in the postictal period (15, 16). In our study, the frequency of headache associated with seizure was 42%, consistent with the literature. We found that these headaches were more frequent in the postictal period, which was also in agreement with the literature.

The frequency of migraine-like headache in patients with headaches associated with seizure has been reported at different frequencies in various studies. Förderreuther et al. reported that 39% of patients with headaches associated with seizure had migraine-like headache (17). Leniger et al. evaluated 341 epilepsy patients for headache and they observed migraine-like headaches associated with seizure in 18.2% of all patients and 55.7% of patients who had headaches associated with seizure (4). In another study, it was observed that migraine-like headache associated with seizures were less frequent, which was different from other studies. However, this was thought to be due to the fact that only patients with temporal lobe epilepsy (TLE), frontal lobe epilepsy (FLE) and occipital lobe epilepsy (OLE) were included in the study, and some had patients received high doses of valproate and zonisamide to reduce headache (18). In our study, we found migraine-like headache associated with seizures were present in 19% of all patients and 45% of patients with headache associated with seizure.

Studies have shown a significant relationship between migraine-like headache associated with seizures and interictal migraine (19,20). In our study, it was observed that interictal migraine was more frequent in those with migraine-like headache associated with seizures. Based on this, we can say that interictal migraine is possibly a predisposing factor for migraine-like headache associated with seizures.

In accordance with the literature (18, 21), the frequency of migraine history in the family was higher in the group of patients with migraine-like headache associated with seizures (31.6%) compared to other groups, but this difference was not statistically significant compared to the groups

of patients with other types of headaches associated with seizures and without headache.

Migraine and seizure-associated headaches are more common in women than in men (16, 22, 23). In our study, it was observed that there was no difference in terms of gender between patients with migraine-like headache associated with seizures, patients with other types of headache associated with seizures, and patients without headaches. This suggests that the mechanism of migraine-like headache associated with seizures may be related to another additional reason specific to the pathophysiology of migraine (4).

Ito et al. found no association between migraine-like postictal headache and gender, age at onset of epilepsy, duration of epilepsy, frequency of seizures, and number of antiepileptics used, but they reported that patients with headache associated with seizures were younger than those without headache (18). In our study, no relation was detected in terms of age, seizure onset age, duration of epilepsy, frequency of seizures and number of antiepileptic drugs used, when we compared patients who had migraine-like headache associated with seizures, those with other types of headache associated with seizures and patients without headaches.

There are conflicting results in studies investigating the relationship between seizure types and the presence of headache associated with seizures. It has been reported in the literature that postictal headaches are more common in generalized seizure than focal seizure, which is attributed to metabolic changes and increased cerebral blood flow following generalized convulsions (19, 24). Secondary generalized tonic-clonic seizure (SJTK) is more common in patients with other types of headaches associated with seizures compared to those with migraine-like headaches associated with seizures (17). In different studies, no relationship was found between headache associated with seizure types and epilepsy syndromes or seizure types (4, 5, 18, 25).

In our study, the mean severity of headache according to VAS was found to be 5.5 \pm 2.2 in patients with headaches associated with seizure. This result shows a moderate pain in accordance with the literature. (20, 22).

Similar to previous studies, the majority of patients with headache associated with seizure (52%) had pain associated with each seizure (3, 22, 24, 26). In addition, in patients with migraine-like headaches associated

with seizures, it was determined that the headaches were frequently associated with seizures, while other types of headache associated with seizure were rarely accompanied by seizures.

In our study, it was seen that preictal headaches were more commonly associated with migraine-like headaches associated with seizures, and aura was associated with preictal headaches rather than postictal headaches. The fact that migraine with aura was the more frequent headache type before seizures suggests that migraine with aura can trigger seizures and that there may be a common mechanism between migraine-like headaches and epilepsy. In our patients with aura detected in the preictal period, because of the absence of aura findings during the one-hour period before the seizure, no diagnosis of migraine aura triggered seizure according to ICHD-3 (International Classification Headache Disorders, 3rd ed.) beta criteria was given.

One of the limitations of this study was that all of the patients included in the study were those who applied to the epilepsy outpatient clinic of a university hospital. This very likely caused a bias towards patients who were difficult to treat. More comprehensive and prospective studies are needed to elucidate the nature of headaches associated with seizures.

As a result, epilepsy and headache are neurological paroxysmal conditions that reduce quality of life. Since the symptoms of epilepsy are rather dramatic, the presence of headaches are often overlooked when not specifically questioned. Questioning the relationships between epilepsy and associated headaches can guide us on the choice of treatment, as well as improve the quality of life of patients suffering from these conditions.

Committee Approval: The present study was approved by Faculty of Medicine of Uludağ University Regional Ethics Committee (2005-18/29).

Informed Consent: Written consent forms were obtained from the participants.

Peer-review: Externally peer-reviewed

Author Contributions: Concept – CH, İB, ÖA; Design – CH, İB, ÖA; Supervision – CH, İB, ÖA; Resources – CH, İB, ÖA; Materials – CH; Data Collection and/or Processing – CH, İB, ÖA; Analysis and/or Interpretation – CH, İB, ÖA; Literature Search – CH, İB, ÖA; Writing Manuscript – CH, ÖA; Critical Review – CH, İB, ÖA.

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